

REMARKS

Applicants respectfully request reconsideration and allowance of this application in view of the following comments.

Claims 17-23 were rejected under 35 USC § 112, first paragraph, as failing to comply with the written description requirement. In response, Applicants respectfully submit that the Examiner's rejection is manifestly incomplete. Although the Examiner says towards the top of page 6 that "Applicants arguments with respect to claims 17-23, 43 have been considered but *are moot* in view of the new ground(s) of rejection," this is clearly incorrect with respect to this rejection, which is a repeat of a rejection made in the previous final rejection. Indeed, the present rejection appears to be the same rejection word-for-word as the rejection made on October 18, 2007. Accordingly, Applicants' arguments in the Pre-Appeal Brief Request for Review are not, in fact, moot. Consequently, the Examiner was required to respond to those arguments.

Applicants respectfully request that, if this rejection is maintained, then the Examiner respond to those arguments in a new Office Action and, moreover, that any such new Office Action not be made final since the Examiner's response should have been included here.

To reiterate, the Examiner finds the specification fails to provide written description for *a modification* of the claimed dyes into a form that permeates the cell membrane. However, Applicants have not claimed any modification of the dyes into

such a form and, therefore, the specification need not contain any written description for such an untemplated modification.

As the prosecution history makes clear, the language is, rather, intended to *exclude* modification of the dyes to a form, such as Wan's, that would prevent the modified dyes from permeating the cell membrane. Such modified dyes would, thus, not be "in a form that permits the fluorescent dye to permeate the membrane," as required by the claims.

Applicants have explained at the top of page 3 of the Pre-Appeal Brief Review Request that the specification *gives examples of suitable dye forms*, for example, dyes dissolved in solutions, that are, in fact, "in a form that permits the fluorescent dye to permeate the membrane." Thus, there is, in fact, clear support for the language in the instant specification.

In this regard, Applicants once again direct the Examiner's attention to *In re Anderson*, 176 USPQ 331, 336 (CCPA 1973), which stands for the proposition that in determining whether an amendment to a claim constitutes new matter, the question is not whether the added word is a word that is used in the application as filed, but whether the concept embodied by the added word is present in the original specification. The concept that the dye is capable of permeating the membrane during use and, thus, in a form that does not defeat this purpose (as Wan's form would defeat it) is clearly set forth in the original specification. Consequently, it does not constitute new matter to add that requirement to the instant claims.

In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw this rejection. An early notice that this rejection has been reconsidered and withdrawn is earnestly solicited.

Claims 17-21, 23 and 43 were rejected under 35 USC § 103(a) as being obvious over Roth et al. (“Roth”), US 5,545,535, in view of Wan et al. (“Wan”), *J. Immunol. Meth.*, 162: 1-7 (1993), in further view of Cubbage, US 5,582,982. In response, Applicants respectfully submit that the cited combination of references does not make out a *prima facie* case of the obviousness of the instant claims. Therefore, Applicants respectfully request that the Examiner reconsider and withdraw this rejection as well.

According to the Examiner:

“It would have been obvious to one of ordinary skills in the art to use an extra dye such Tryptan blue as taught in Wan to quench extracellular fluorescence in the method of Roth because Roth uses a combination of four fluorescent dyes to stain cells and thus there would be plenty of extracellular fluorescence which would cause non-specific background light, and Tryptan blue can completely quench extracellular fluorescence.”

See the second paragraph on page 4 of the Office Action.

Applicants respectfully disagree.

According to Roth, an important aim of the invention described therein is the detection of ***dead cells or membrane-compromised cells***. This can be derived from the definition of viable/dead cells at column 5, lines 36-53 in combination with, for example,

column 22, lines 1-15, where viability of single cells shall be determined. Such determination naturally includes detection of both viable and dead cells. “Viable” cells are defined by Roth at column 5, lines 36-39, as those having “an intact cell membrane.” “Dead” cells are defined by Roth at column 5, lines 43-45, as those “where the cell membrane has been *irreversibly disrupted*.” Roth also characterizes these “dead” cells as “‘membrane-compromised’ cells.” *Id.* Also, in the abstract, Roth describes the fluorescent dyes of formula I to IV with respect to their impact on dead bacteria or on cells with comprised plasma membrane integrity.

But exactly because Roth’s assays involves detection of these dead and membrane-compromised cells, a person skilled in the art would not, in fact, have been motivated to add Trypan blue or any other masking dye to Roth’s assay. Such masking dye would have been expected not only to stain the ambience of the cells and, thus, to reduce the background fluorescence, but would also have been expected *to permeate into the dead cells*, i.e., into the cells “where the cell membrane has been *irreversibly disrupted*” (see, again, column 5, lines 43-45), and also *to quench the signal from these cells*. Such a state of affairs would have rendered Roth’s assay unworkable and the results obtained therefrom inaccurate.

In short, modifying Roth to include a masking dye to quench the background fluorescent would have rendered Roth *inoperable for its intended purpose* since such masking dye would also have permeated into the dead cells, which have a disrupted membrane, and quenched the signal from these cells. As set forth in MPEP § 2143.01 (V):

“If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, *there is no suggestion or motivation to make the proposed modification.*”

This legal principle is well-settled and finds ample support in the case law. *See, In re Kramer*, 18 USPQ2d 1415, 1416 (Fed. Cir. 1991) (“[I]t is equally true that if the *teachings* of a prior art reference would lead one skilled in the art to make a modification which would render another prior art device inoperable, then such a modification would generally not be obvious (*italics in original*).”) *See, also, In re Gordon*, 221 USPQ 1125, 1127 (Fed. Cir. 1984) (Apparatus, which was required to be turned upside down to meet the terms of the claims, but, by such action would be “rendered inoperable for its intended purpose,” in effect “teaches away from the board’s proposed modification.”)

Respectfully, the Examiner is wrong in asserting that the combination of Roth, Wan and Cubbage would have led to the present invention of the rejected claims. The fact of the matter is that persons skilled in the art would not, in fact, have added a masking dye to Roth’s assay as allegedly taught by Wan, since, as explained above, such addition would have rendered Roth’s assay inoperative for its intended purpose since such masking dye would have been expected to interfere with the signal from Roth’s dead, membrane-disrupted cells.

In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw this rejection as well. An early notice that this rejection has been reconsidered and withdrawn is earnestly solicited.

Finally, claim 22 was rejected under 35 USC § 103(a) as being obvious over Roth in view of Wan and further in view of Cubbage and still further in view of Van Aken, US 5,489,537. In response, Applicants point out that this rejection was dependent upon the combination of Roth, Wan and Cubbage making out a *prima facie* case of the obviousness of the broader claims, which Applicants have shown above is not, in fact, the case. Van Aken is relied upon simply to teach Brilliant Black as a fluorescent dye. There is nothing in Van Aken that overcomes the fact that the Examiner's proposed combination of Roth and Wan would have rendered Roth inoperative for its intended purpose and, therefore, is an improper combination. Consequently, the combination of Roth, Wan, Cubbage and Van Aken likewise fails to make out a *prima facie* case of the obviousness of claim 22.

In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw this rejection as well. An early notice that this rejection has also been reconsidered and withdrawn is earnestly solicited.

Applicants believe that the foregoing constitutes a bona fide response to all outstanding objections and rejections.

As this application has been pending an inordinate period of time, i.e., *since September 2001*, Applicants would appreciate receiving an immediate Notice of Allowance. However, should any issue(s) of a minor nature remain, the Examiner is respectfully requested to telephone the undersigned at telephone number (212) 808-0700 so that the issue(s) might be promptly resolved.

Early and favorable action is earnestly solicited.

Respectfully submitted,

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